MEMORANDUM OF MEETING

Date: January 30, 1987

Drug: AZT: NDA 19-655; NDA 19-656

Attendees:

Paul Parkman, M.D.	HFN-1
Jim Bilstad, M.D.	HFN-801
Don McLearn	HFN-1
Elaine Esber, M.D.	HFN-800
Edward Tabor, M.D.	HFN-815
Ellen Cooper, M.D.	HFN-815
George Stanley, M.D.	HFN-815
Jackie Knight	HFN-815
Sammie Young	HFN-301
Robert O'Neill, Ph.D.	HFN-710
Lawrence Hauptman, Ph.D.	HFN-710
Ross Laderman	HFN-340
Joel Kuritsky, Ph.D.	HFN-733
Frances Kelsey, M.D.	HFN-340
Alan Lisook, M.D.	HFN-340
Antoine El-Hage	HFN-340

This in-house meeting was held to consider whether or not to exclude the data from the Boston center, (Robert Schooley, P.I.) from the analysis of the AZT multi-center trial. Since this one multi-center trial is the only study to support approval of the NDAs for AZT and since the total number of patients is relatively small, a decision to exclude this center, while unlikely to change the significance of the major efficacy variables (death and time to first opportunistic infection) for all patients, could affect the outcome of the various subgroup analyses (such as AIDS vs. ARC).

Dr. Bilstad opened the meeting by stating that the implications of excluding the Boston center are greater than usual because of the high visibility of this particular drug and that we should base our decision on whether or not the deficiencies found would influence the validity of the data.

Mr. El-Hage outlined the deficiencies found by the FDA inspectors including poor drug accountability, data added to case report forms (CRFs) after the fact and data entries on the CRFs changed by Burroughs-Wellcome's clinical monitor, Ron Beitman, without the principal investigator's (Dr. Schooley) documented approval.

The inspection report indicates that Mr. Beitman transferred data from the patient diaries to the CRFs and "filled in" missing entries.

Burroughs Wellcome had been advised of these deviations from the proper conduct of a study and their January 28, 1987 response to the problems listed in the 483 issued to Dr. Schooley, at this center, was also discussed.

The questions surrounding drug accountability were satisfactorily resolved; it appears that the patients were properly randomized and received the appropriate medication. Further, everyone agreed that Mr. Beitman's changes on the CRFs seemed to be an attempt to "clean-up" the study records and that there is no indication of intent to falsify data.

Dr. Kelsey said that Scientific Investigations would send Dr. Schooley a regulatory letter asking him for a written explanation of why the study was conducted so carelessly, (VAI 3) but that he would not be disqualified as an investigator since there was no malicious intent.

There was more discussion of the inspector's list of deviations from standard procedures in the conduct of a clinical investigation. Everyone agreed that no single deficiency was egregious enough to warrant deleting the data from this center from the total data base, but there was no consensus on when or whether multiple minor deviations become grounds to "disqualify" a study. Everyone agreed the decision is a close call. Dr. Cooper indicated that the original protocol design, the design and format of the case report forms and contact with BW physicians when questions arose permitted broad discretion on the part of the investigators regarding judgments as to possible entry criteria violations, reporting of disease symptoms and possible adverse drug experiences, use of concomitant medications, dose reductions, discontinuations, and restarts, documentation of end points and adverse events occurring in another hospital, etc. Dr. Cooper also asked how the Agency has handled the question of acceptability of data from a center in which multiple violations of standard investigational drug study procedures has occurred.

In regard to this matter, two questions arose:

1. How did the conduct of the study at this center compare with the other centers and

2. did the recording and record changing irregularities occur at the two other centers for which Mr. Beitman was clinical monitor.

Mr. El-Hage indicated that since written reports of the inspections have not been received, he could not answer those questions.

Dr. O'Neill stated that his group had already analyzed the data with and without Schooley's data and it made no difference in the significance of the major efficacy end-points (mortality and occurrence of first OI). He suggested that we do the analyses both ways for some of the lesser efficacy parameters then discuss this approach in the Summary Basis of Approval. Dr. Bilstad stated that Burroughs Wellcome had estimated that it would take the an additional two months to reanalyze the data without the Schooley center.

There was more discussion of whether or not to drop the center or drop-out individual patients but no firm consensus was reached. Again, the participants agreed that this is a close call with Dr. Parkman and Dr. Bilstad leaning toward leaving the center in and Dr. Tabor and Dr. Cooper closely questioning the basis for this recommendation. It was finally decided that the situation would be presented to Dr. Young for his input.

It was also agreed that a second meeting would be scheduled to discuss issues common to all the study centers e.g. prophylactic medication for OIs, dose reductions and discontinuations not recorded on the CRFs, poor screening of patients, etc.

The meeting ended.

J Knight

Jacqueline Knight

cc:
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ORIG. NDA 19-656
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HFN-301/SYoung
HFN-340/FKelsey
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HFN-340/AEl-Hage
HFN-340/RLaderman
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HFN-710/LHauptman
HFN-733/JKuritsky
HFN-800/EEsber
HFN-800/DMcLearn
HFN-801/JBilstad
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